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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,286	08/02/2001	Xiaobin Zhao	0623.1110001/JMC/MGP	3882

26111 7590 05/20/2003

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EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	12

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,286	ZHAO, XIAOBIN	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,15-19 and 21* is/are rejected.

7)☒ Claim(s) *13,14 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Objections/Rejections Set For the in Office Action dated November 25, 2002

1. Claim 10 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 depends from claim 9 which is drawn to process of claim 1 wherein the cross-linking of each type of functional group is effected sequentially. Claim 10 is drawn to the process of claim 9 wherein HA is cross-linked via a first functional group and subsequently further cross-linked via a second chemical entity. The examiner interprets the "sequential steps" of the process as being performed by cross-linking HA via a first functional group and subsequently further cross-linking said HA via a second chemical entity.

2. Claims 13-14 and 20 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

3. Applicant was advised that should claim 15 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. Claims 1-12, 15-19, and 21 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for double cross-linked HA, does not reasonably provide enablement for multiple cross-linked HA wherein more than two chemically distinct cross-links between HA molecules are present. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claims 1-12 are drawn to a process for preparing multiple cross-linked derivatives of hyaluronic acid comprising covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with

one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules. Claims 15-19 and 21 are drawn to multiple cross-linked derivatives of hyaluronic acid wherein HA is cross-linked by two or more chemically distinct entities.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to multiple cross-linked derivatives of hyaluronic acid comprising covalently cross-linking HA via two or more different functional groups.

Cross-linked HA is known in the art. Balazs et al. U.S. Patent 4,582,865 teaches cross-linked gels of hyaluronic acid. HA cross-linked via ester bonds are taught by della Valle et al. U.S. 4,957,744.

A person of ordinary skill in the art would be an organic or polymer chemist having a M.S. degree or higher.

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to enable the making of cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. The specification does not teach cross-linking of HA via more than two chemically distinct entities or bonds.

The working examples in the instant specification are limited the production of double cross-linked HA.

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation multiple cross-linked HA wherein more than two chemically distinct cross-links between HA molecules are present.

5. Claim 21 was rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cross-linked HA in the form of a film or gel, does not reasonably provide enablement for all products comprising said cross-lined HA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claim 21 is drawn to multiple cross-linked derivatives of hyaluronic acid wherein HA is cross-linked by two or more chemically distinct entities.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to multiple cross-linked derivatives of hyaluronic acid comprising covalently cross-linking HA via two or more different functional groups.

Cross-linked HA is known in the art. Balazs et al. U.S. Patent 4,582,865 teaches cross-linked gels of hyaluronic acid. HA cross-linked via ester bonds are taught by della Valle et al. U.S. 4,957,744.

A person of ordinary skill in the art would be an organic or polymer chemist having a M.S. degree or higher.

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to enable the making of products of cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities.

The working examples in the instant specification are limited the production of double cross-linked HA. There are no examples of products comprising multiple cross-linked HA.

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of products comprising multiple cross-linked HA wherein more than two chemically distinct cross-links between HA molecules are present.

Applicant's Response dated February 24, 2003

6. In the Response filed February 24, 2003, claim 10 was canceled. Applicant presented arguments directed to the objection of claims 13-14, 16, and 20 and the rejection of claims 1-12, 15-19, and 21 under 35 U.S.C. § 112, first paragraph. Claims 1-9 and 11-21 are pending. An action on the merits of claims 1-9 and 11-21 is contained herein below.

7. The cancellation of claim 10 in the Response dated February 24, 2003 has rendered the rejection of said claim moot.

8. Applicant's arguments with respect to claims 1-9 and 11-21 have been considered but are moot in view of the new ground(s) of rejection.

Claim Objections

9. Claims 13-14 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 11-12, 15-19, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A written description analysis involves three principle factors:

1. Field of the invention and predictability of the art
2. Breadth of the claims
3. For each claimed species/genus, possession of claimed invention at the time of the filing.

Claims 1-9 and 11-12 are drawn to a process for preparing multiple cross-linked derivatives of hyaluronic acid (HA) comprising covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules. Claims 15-19 and 21 are drawn to multiple cross-linked derivatives of hyaluronic acid wherein HA is cross-linked by two or more chemically distinct entities.

The specification teaches the production of double cross-linked HA. The support in the specification is not adequate for the claim to the production of multiple cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. Pages 7-8 of the specification teach:

> It will be appreciated that when the two or more functional bonds according to the invention are formed sequentially, i.e. in a multi-stage reaction, the cross-link formed in the first stage of the reaction should be sufficiently strong to withstand the reaction conditions needed to form the second or subsequent cross-link(s). Thus, the stronger of the two (or more) bonds should be formed first. This will be

> readily apparent to the skilled worker and if necessary can be determined by means of routine experimentation.

This "routine experimentation" is not seen to be routine. No guidance is given in respect to determining the "stronger bond". The specification does preferentially teach formation of an ether bond first, but this information does not provide any guidance as to forming a third or higher cross-link of HA. At each stage of this multi-step process, an additional set of concerns is raised as a new set of reactants will be employed (the product of the prior step, cross-linking agent, and catalyst if necessary) and an additional bond must be "protected". What type of bond should be formed next? What functional group(s) should be employed? What cross-linking agent should be employed? What reaction conditions should be employed (i.e. temperature, pH, solvent, etc.)?

The written description requirement for a claimed genus may be satisfied through sufficient description of an adequate representation of species by functional characteristics sufficient to show the applicant was in possession of the claimed genus. There are a great number of compounds which may be envisioned as being multiple cross-linked HA, each being produced by a process employing a certain degree of specificity for which there is not seen adequate support for in the instant disclosure. There is limited predictability in the art in regards chemical reactivates of any functional group (i.e. solvent effects, temperature, steric hindrance, pH, etc.). To provide adequate support for the breadth of the claims, applicant would have to provide sufficient evidence showing the production of multiple cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. The

specification is seen to provide for the formation of double cross-linked HA; however, this does not correlate via art recognized evidence or adequate support in the instant disclosure to the production of multiple cross-linked derivatives of hyaluronic acid by a process comprising covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules as broadly claimed. An adequate representation of species requires that the species which are expressly described and recognized in the art as representative of the entire genus. What constitutes a "representative number" is an inverse function of the predictability in the art in question. As such, there is not seen any data or correlative prior art evidence which supports applicant's claim to the production of multiple cross-linked derivatives of HA as claimed at the time of filing.

Conclusion

12. Claims 1-9 and 11-21 are pending. Claims 1-9, 11-12, 15-19, and 21 are rejected. Claims 13-14 and 20 are objected to. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

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May 19, 2003